Protocol *B5201006*

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP SINGLE-DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF INTRAVENOUS RIVIPANSEL (PF-06460031) IN SUBJECTS WITH MODERATE HEPATIC IMPAIRMENT AND IN HEALTHY SUBJECTS WITH NORMAL HEPATIC FUNCTION

Statistical Analysis Plan
(SAP)

Version: **1.0**

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Date: **02 SEP 2016**

DMB02-GSOP-RF18 2.0 STATISTICAL ANALYSIS PLAN TEMPLATE FOR HEPATIC IMPAIRMENT STUDY
30-Jun-2015

[redacted]
TMF Doc ID: 98.03

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	Aug 03rd, 2016	PPD	This is an initial version based on the final protocol dated on 27Jun2016.

List of Reviewers

Role Name	Reviewer's Name
Clinician	PPD
Clin Pharm Clinician	
Clinical Lead	
Clinical Statistician	
Regulatory Lead	
Clinical Programming	
Clinical Operations Study Team Lead	
Data Analysis & Reporting Lead	

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

Rivipansel is being developed as a pan-selectin antagonist for the treatment of vaso-occlusive crisis (VOC) in subjects with Sickle Cell Disease (SCD). Both children and adults are affected, and greater mortality is seen in those with more severe disease.

Although rivipansel is known to be primarily eliminated by the kidney (>90% of dose excreted in urine based on data from the Single Ascending Dose study GMI-1070-101), hepatic function can have an effect on the PK of drugs for which the excretion is primarily renal. This study is therefore being conducted to evaluate the effect of hepatic impairment on the PK, safety and tolerability of rivipansel. Results from this study will be used in conjunction with collective safety, efficacy, and PK/pharmacodynamic (PD) data from other rivipansel studies to provide recommendations on dosing for subjects with hepatic impairment.

A single 840 mg dose of IV rivipansel will be used in this study as it is the dose selected for maintenance dosing in the rivipansel Phase 3 program. IV doses of rivipansel as high as 4 g (as a single dose) have been well tolerated in healthy volunteers. In the Phase 2 study multiple doses, using a loading dose of 40 mg/kg followed by doses of 20 mg/kg given every 12 hours for up to 7 days were also well tolerated. Therefore, it is expected that potential increases in exposure due to hepatic impairment with a single dose of 840 mg should not pose a safety concern. Single-dose administration was chosen because time-independent PK of rivipansel have been demonstrated at the anticipated concentrations, and thus single-dose PK will be able to adequately predict multiple-dose PK.

2.1. Study Design

*This study is a Phase 1 open-label, single-dose, single-treatment, non-randomized study of rivipansel in subjects with moderate hepatic impairment and healthy subjects with normal hepatic function. Since rivipansel is primarily eliminated renally, a reduced study design with two groups (control subjects and subjects with moderate hepatic impairment) was considered adequate to characterize the PK in subjects with hepatic impairment. The Child-Pugh Score will be utilized to assess entry criteria and to assign subjects to the appropriate hepatic-impairment group. Child-Pugh assessments will be performed within the 14 days prior to study medication administration and Day 0 (baseline). Subjects should satisfy the criteria for Child-Pugh classification as Moderate Hepatic Impairment (Class B Score 7-9) for both assessments in order to be enrolled into the study. The subjects' hepatic function will be ranked based on clinical signs and liver function test results (*Table 1*).*

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Table 1. Child-Pugh Classification

Assessment Parameters	*Assigned Score for Observed Findings*		
	1 point	***2 points***	***3 points***
Encephalopathy Grade [a]	*0*	*1 or 2*	*3 or 4*
Ascites	*Absent*	*Slight*	*Moderate*
Serum bilirubin (mg/dL)	*<2*	*2 to 3*	*>3*
Serum albumin (g/dL)	*>3.5*	*2.8 to 3.5*	*<2.8*
Prothrombin time (seconds prolonged)	*<4*	*4 to 6*	*>6*
Classification of clinical severity: *Mild (Class A): Total score 5-6 points* *Moderate (Class B): Total score 7-9 points* *Severe (Class C): Total score >9 points*			

a. Grade 0: Normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per sec) waves.
Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slow waves.
Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

A total of approximately 16 subjects will be enrolled; 8 subjects with moderate hepatic impairment and 8 healthy subjects with normal hepatic function. Healthy subjects with normal hepatic function will be enrolled after all of the subjects with moderate hepatic impairment have completed the in-patient portion of the study and will be matched for age, weight, and gender to the mean demographics of subjects in the moderate hepatic impairment group. Healthy subjects with normal hepatic function will be enrolled to enable comparison of PK parameters between healthy subjects and subjects with moderate hepatic impairment.

Subjects who withdraw from the normal hepatic function or moderate hepatic impairment groups for non-safety related reasons and who are considered to be non-evaluable with respect to the primary PK objective will be replaced at the discretion of the investigator and sponsor such that the number of completed subjects in each group equals eight.

2.2. Study Objectives

Primary Objectives

- *To evaluate the effect of moderate hepatic impairment on the PK of rivipansel following a single 840 mg IV dose.*

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- *To evaluate the safety and tolerability of a single 840 mg IV dose of rivipansel in subjects with moderate hepatic impairment and in healthy subjects with normal hepatic function.*

Secondary Objective

- *To evaluate the effect of moderate hepatic impairment on additional PK parameters for rivipansel following a single 840 mg IV dose.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned. Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all subjects treated who have at least 1 concentration.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all subjects treated who have at least 1 of the PK parameters of primary interest.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

5.4. Other Analysis Sets

None.

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5.5. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are randomized but not treated.

5.6. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Any events occurring or increasing in severity following start of treatment will be counted as treatment emergent.

Events that occur in the Follow-up period will be counted as treatment emergent and causality attributed to the treatment taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *Adverse events,*
- *Laboratory data,*
- *Vital signs data,*
- *ECG results.*

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6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-06460031will be collected according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06460031 (if possible) from the concentration-time data using standard non-compartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-06460031
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
$t_{1/2}$*	R	D
CL*	ln	D
V_{ss}*	ln	D

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

6.3.2. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. Concentrations below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

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7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been recorded as ND (ie not done) or NS (ie no sample),

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular hepatic function group with ≥3 evaluable measurements. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

The effect of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated differences between the Test (impaired hepatic function group) and the Reference (normal hepatic function group) PK parameters using a one-way ANOVA model based on natural log transformed data.

8.2. Statistical Analyses

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} between normal hepatic function group and the impaired hepatic function group. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted

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mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The normal hepatic function group will be the Reference group and the impaired hepatic function group will be Test group.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals, but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analyses will be provided in the report of the study.

The following PK parameters will be summarized by hepatic function group:

Table 3. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CL and V_{ss}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last} and C_{max}) will be presented by hepatic function group and overlaid with geometric means.

Supporting data from the estimation of t½ and AUC_{inf} will be listed by hepatic function group: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

Presentations for PF-06460031 concentrations will include:

- A listing of all concentrations sorted by hepatic function group (present in heading), subject id and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be provided in a separate listing.

- A summary of concentrations by hepatic function group and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

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- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function group (both hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by hepatic function group (both hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time postdose).

- Individual concentration time plots by hepatic function group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each hepatic function group per scale).

For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

8.3. Safety Analysis

A set of summary tables split by hepatic function group will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06460031.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by hepatic function group.

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A break-down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Subject discontinuations due to adverse events will be detailed and summarized by hepatic function group.

Data will be reported in accordance with the sponsor reporting standards.

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8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by hepatic function group.

8.3.5. Laboratory Data

Laboratory data will be listed and out of range values will be summarized in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

The baseline measurement is the last pre-dose measurement.

These data will be listed and out of range values will be summarized in accordance with the sponsor reporting standards.

8.3.7. ECG Data

The baseline measurement is the pre-dose measurement.

These data will be listed and out of range values will be summarized in accordance with the sponsor reporting standards.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, , reproductive status and, and alcohol test will be obtained at Screening.

These data will not be brought in-house, and therefore will not be listed.

9. REFERENCES

None.

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10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC Mixed code is provided below:

```
proc mixed data=tab.pk  covtest alpha=0.1;
        class group;
        model l&var=group/ alpha=0.1 CL DDFM=KR;
        lsmeans group;
        estimate 'Moderate vs Normal'          group 1 -1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;

run;

/* Letter assignments for group within the estimate statement above are as follows;

A = Moderate (Test);
B = Normal (Reference);

*/;
```

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